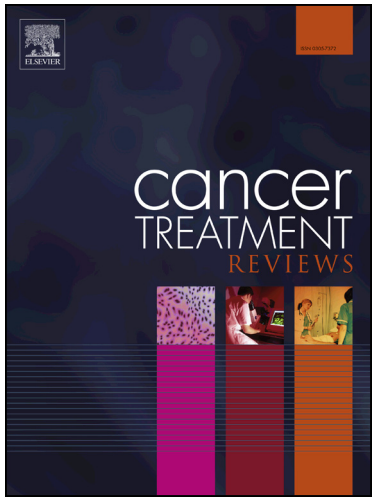

Systematic or Meta-analysis Studies

Increased life expectancy as a result of non-hormonal targeted therapies for HER2 or hormone receptor positive metastatic breast cancer: a systematic review and meta-analysis

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PII: S0305-7372(17)30001-4
DOI: http://dx.doi.org/10.1016/j.ctrv.2017.01.001
Reference: YCTRV 1592

To appear in: *Cancer Treatment Reviews Cancer Treatment Reviews*

Received Date: 4 October 2016
Revised Date: 2 January 2017
Accepted Date: 3 January 2017

Please cite this article as: Koleva-Kolarova, R.G., Oktora, M.P., Robijn, A.L., Greuter, M.J., Reyners, A.K., Buskens, E., Bock, G.H.d., Increased life expectancy as a result of non-hormonal targeted therapies for HER2 or hormone receptor positive metastatic breast cancer: a systematic review and meta-analysis, *Cancer Treatment Reviews Cancer Treatment Reviews* (2017), doi: http://dx.doi.org/10.1016/j.ctrv.2017.01.001

Increased life expectancy as a result of non-hormonal targeted therapies for HER2 or hormone receptor positive metastatic breast cancer: a systematic review and meta-analysis

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Increased life expectancy as a result of non-hormonal targeted therapies for HER2 or hormone receptor positive metastatic breast cancer: a systematic review and meta-analysis

Abstract

This article aimed to assess the clinical effectiveness of non-hormonal targeted therapies (TTs) in terms of increase of median progression-free survival (PFS) and overall survival (OS) in receptor-positive metastatic breast cancer (MBC) patients by performing a systematic review and meta-analysis. We systematically searched relevant randomized controlled trials and extracted data about number of patients on targeted and comparator therapy, receptor status, line of treatment, median PFS and OS, p values, hazard ratios (HRs) and 95% confidence intervals (CI). Inverse variance was used to estimate pooled HRs, chi-square test for heterogeneity and Jadad scale for quality were applied. Thirty eight studies (n=17,192 patients) were eligible for inclusion. TTs added 3.3 months to the median PFS [0.7–9.6; HRs 0.74, 95% CI 0.71–0.77] of receptor-positive MBC patients and prolonged their median OS with 3.5 months [0–4.7; HRs 0.90, 95% CI 0.82–0.98]. The highest increase in median PFS of 3.6 months was found in HER2-/HR+ patients, while the highest increase in median OS of 7.2 months was observed in HER2+/mixed hormone receptor (HR) status patients. First-line TTs were most effective in increasing the median PFS in the HR+/HER2- group with 2.0 months, and in the HER2+/HR-mixed group by adding 4.7 months to the median OS. Second-line TTs were most effective for HER2-/HR+ patients by adding 2.6 months to their PFS, and for HER2+/HR-mixed patients by adding 3.1 months to their median OS. Albeit small, the gain in months of median PFS and median OS was significant. Importantly, the results reported show large variation, and thus routinely applying a personalized approach seems warranted.

Keywords: breast neoplasm; molecular targeted therapy; human epidermal growth factor receptor 2; estrogen receptors; progesterone receptors; survival analysis.

Introduction

Advanced breast cancer is encountered in around 5-10% of patients with primary breast cancers [1], and another 10% of the patients develop distant recurrence within 5 years after primary disease and treatment [2,3]. Once breast cancer has metastasized to distant locations, it is generally considered amenable to palliative rather than curative care. Therefore, the goals of treatment at this later stage are focused on delaying the progression of the metastatic disease, relief of cancer-related symptoms and maintaining quality of life [1].

The majority of patients with metastatic breast cancer (MBC) are subjected to targeted therapy (TT) depending on the presence of a positive receptor status of the metastasis (human epidermal growth factor receptor (HER2) and/or hormone receptor (HR) – estrogen (ER) and progesterone (PR) [1]. Targeted treatment entails anti-HER2 agents (for HER2-positive disease), hormone therapy and anti-HR agents alone or in combination (for HR-positive disease) [1]. Significant advances in molecular targeted therapies and the development of new treatment combinations can offer a personalized and less aggressive approach of managing patients with metastatic disease that have overexpressing receptor status [4,5]. Withholding certain a priori ineffective treatments in some patients while immediately switching to other last resort treatments in others can have a positive impact on their survival. TTs have been tested in randomized controlled trials (RCTs) to assess clinical effectiveness in terms of time to disease progression and overall survival [6]. Most of the investigated treatments suggest that TTs could prolong life of MBC patients [7]. However, the extent to which TTs could increase the survival of MBC patients is yet unclear.

Previous systematic reviews and meta-analyses have demonstrated that the addition of TT to chemo- and endocrine therapies significantly improved the overall survival (OS) and the progression-free survival (PFS) of HER2-positive and/or HR+ MBC patients [6,7]. Others reported increased efficacy of trastuzumab in combination with chemotherapy on the median OS [8] and improved OS of these patients when treated with lapatinib [9]. Although these previous reviews clearly demonstrate that TTs improved survival, they did not estimate the absolute effects in terms of duration of time (i.e. months) added to the life of these patients. Since this information is crucial for future cost-effectiveness studies, the aim of this analysis was to assess the clinical effectiveness of non-hormonal TTs in terms of increase in months in median PFS and OS of patients diagnosed with advanced or MBC by performing a systematic review and meta-analysis of published RCTs.

Methods

This systematic review adhered to the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [10] and followed a predetermined search strategy and selection criteria developed by two reviewers (GHdB and RGKK).

Data sources and search strategy

A comprehensive search of PubMed was initially performed on 6 July 2015, and updated on 21 December 2016. The search algorithm was designed by an experienced librarian (DGvI) and included the following keywords and Mesh terms: breast neoplasms, breast, survival analysis, survival rate, survival, treatment outcome, mortality, trastuzumab, trastuzumab emtansine, lapatinib, pertuzumab, bevacizumab, everolimus, palbociclib.

Eligibility criteria

Articles were considered if they described RCTs which enrolled women with advanced and/or metastatic breast cancer and compared approved by the Food and Drug Agency (FDA) and the European Medicines Agency (EMA) non-hormonal TTs (trastuzumab, trastuzumab emtansine, lapatinib, pertuzumab, bevacizumab, everolimus, palbociclib) to other types of treatment or placebo. Studies were selected if the reference arm also included TT or hormonal therapy, as long as the intervention arm included the approved TT of interest, and the arms did not compare one and the same TT. Only trials that reported the outcomes of interest (PFS and/or OS) were included irrespective of the phase of the study. The articles which used different types of study design and lacked original data (reviews, editorials, etc.) were excluded. Studies which were not reported in English or their abstract and full text could not be obtained were also excluded. In case of several articles describing the same trial, the most recent publication was selected and included in the analyses.

Study selection and data extraction

Three reviewers (MPO, ALR and RGKK) independently assessed each title and abstract for eligibility. Included trials were retrieved as full texts and screened for duplicates.

Disagreement at any level was resolved by consultation with a fourth reviewer (GHdB). The three reviewers independently performed the data extraction and retrieved study details from the articles by a predefined questionnaire which included type of trial, line of treatment, receptor status of the metastatic disease, targeted and comparator therapies, and number of patients. The extracted results of interest encompassed: time to outcome (PFS and OS) – median and range, p values, hazard ratios (HRs), and 95% confidence intervals (CI) (Table 1, Table 2, Figure 2 and Figure 3). HRs were defined as the risk of recurrence or further spread of the metastatic disease. PFS was defined as the time of randomization until the time of disease progression or death from any cause. OS was defined as the time from randomization until the time of death from any cause.

Statistical analysis

The HRs outcomes were pooled into a forest plot in Review Manager (RevMan) [11] to determine the overall HRs effect between the TTs and the comparator therapies. The pooled HRs were calculated by applying random effects model. The reported outcomes of interest (PFS and OS) from the studies were used to determine the median and the range of PFS and OS from all studies for the TT and the comparator arms. To test whether there was a difference in survival depending on the receptor status (HR or HER2), line of treatment or type of TT, subgroup-analyses were performed for HER2-positive and HR-positive groups of patients, per line of treatment and per type of TT. For this purpose all reported outcomes were transformed into months. Immature and interim PFS and OS results were not included into the analyses. A chi-square test for heterogeneity was used to test for homogeneity between studies and a p-value of 0.10 was applied [12].

Assessment of risk of bias

The Jadad scale [13] was used to assess the quality of the selected RCTs. The mean and the median, and the range of the Jadad score was reported for all studies.

Results

Selection of studies

Six hundred and fifty three hits appeared in PubMed on 21 December 2016 with the search strategy described previously. Four hundred and fourty seven articles were excluded after screening the titles and abstracts as not matching the eligibility criteria. The full text of the remaining 206 articles was examined and 38 RCTs published in 40 articles which contained PFS and/or OS as outcome were identified as being eligible to be included in the review (n=17,192 patients, Figure 1) [14–53].

Type of targeted therapy

The most commonly investigated TTs in the selected RCTs including large groups of patient population were trastuzumab, bevacizumab and lapatinib, while trastuzumab emtansine, pertuzumab, everolimus and palbociclib were less tested and the number of patients included was smaller (Table 1).

Progression-free survival – hazard ratios, median and range

The pooled hazard ratio was 0.74 (95% CI 0.71–0.77), indicating that overall TTs improved significantly the median PFS in patients with receptor-positive MBC (Figure 2). TTs increased PFS with 37%. In general, TTs had longer median PFS than the comparator strategies. The median PFS for all studies in receptor-positive MB C patients was 9.0 months [2.6–24.8] for the TT arms and 5.7 months [1.9–15.2] for the comparator arms. Overall the application of TTs in receptor-positive MBC patients added 3.3 months [0.7–9.6] to the median PFS of these patients (Table 1, Table 2).

The analysis for the subgroup of patients with HER2-positive and mixed HR status disease demonstrated that the use of TTs added 2.4 months [0.7–3.5] to the median PFS of these patients (HRs 0.76, 95% CI 0.72–0.80). First-line TTs in this subgroup showed the same PFS as compared to second-line and beyond TTs (Table 1, Table 2, Figure 2). Everolimus and trastuzumab emtansine demonstrated longer median PFS in MBC patients with HER2-positive and HR-mixed disease as compared to trastuzumab and pertuzumab containing regimens, and lapatinib.

The analysis for the subgroup of patients with HER2-negative and HR-positive disease revealed that the use of TTs added 3.6 months [1.8–10.3] to the PFS of these patients (HRs 0.71, 95% CI 0.67–0.75). First-line TTs in this subgroup showed shorter median PFS as compared to second-line and beyond TTs (Table 1; Figure 2). In the same subgroup palbociclib demonstrated the highest increase in median PFS, followed by bevacizumab and everolimus (Table 1, Table 2).

The heterogeneity of all studies was 84%, Chi^2=250.59 and p<0.00001, indicating substantial diversity among studies.

Overall survival – hazard ratios, median and range

The pooled hazard ratio was 0.90, 95% CI (0.82–0.98), indicating that overall TTs improved significantly the median OS in patients with receptor-positive MBC (Figure 3). TTs increased the median OS with 12%. In general, the investigational study arms including TTs showed longer median OS than the comparator strategies. The median OS of all studies in receptor-positive MBC patients was 28.6 months [14–56.5] for the TT arms and 25.1 months [9.5–51.8] for the comparator arms. The application of TTs in receptor-positive MBC patients added 3.5 months [0–4.7] to their survival (Table 1, Table 2).

The analysis for the subgroup of patients with HER2-positive and mixed HR status disease demonstrated that the use of TTs added 7.2 months [4.5–15.7] to the median OS of these patients (HRs 0.89, 95% CI 0.77–1.02). First-line TTs showed longer median OS as compared to second-line and beyond TTs and added more to the survival of these patients (4.7 months first-line vs. 3.1 months second-line – Table 1, Table 2, Figure 3). In the same subgroup investigational regimens containing trastuzumab, pertuzumab, trastuzumab emtansine and lapatinib demonstrated superior median OS than the comparator arms' regimens (Table 1, Table 2).

The analysis for the subgroup of patients with HER2-negative and HR-positive disease revealed that the use of TTs added 3.6 months [0.6–not estimated] to the median OS of these patients (HRs 0.91, 95% CI 0.84–0.99). First-line TTs showed longer median OS as compared to second-line and beyond TTs, but did not add to the survival of these patients, (Table 1, Table 2, Figure 3). In the same subgroup bevacizumab demonstrated the highest increase in median OS. Lapatinib and palbociclib showed improved median OS, while everolimus did not reach projected OS (Table 1, Table 2).

The heterogeneity of all studies was 59%, Chi^2=64.06 and p<0.0001, indicating moderate to substantial diversity among studies.

Assessment of risk of bias

The mean Jadad score of the RCTs used in this review was 3.0 (median 3, range 1 – 5).

Discussion

This analysis demonstrated that the application of non-hormonal TTs in metastatic breast cancer results in an increase in PFS which is most prominent in patients with HER2-negative and HR-positive disease, whereas OS increase was most prominent in patients with HER2-positive disease and mixed HR status disease.

The pooled HRs showed that TTs significantly prolonged the median PFS and OS as compared to other therapies. However, in absolute length of time (i.e. months) these median prolongations of PFS and OS appeared less impressive. TTs were most beneficial for the median PFS of patients with HER2-negative and HR-positive disease and for the median OS of patients with HER2-positive and mixed HR-disease. It should be noted, though, that a large variation was observed in the minimum and maximum ranges of PFS and OS for both the TT and the comparator arms, as well as per receptor status and line of treatment. Therefore, determination of the receptor status of the tumors is important for personalized selection of therapy.

Having in mind the incidence of breast cancer and the fact that MBC is considered incurable [1], even a small increase in PFS and OS could be beneficial for patients with distant relapse. Our findings confirmed the effectiveness of non-hormonal TTs in MBC patients with receptor positive, either HER2 or HR, disease. Findings by other studies suggested that increase in survival benefits was accompanied by increase in adverse effects [6,7,54,55], which can impact negatively the quality of life of MBC patients. Therefore, in clinical practice it is important to consider different dose adjustments and different combinations of treatment options.

A review by Kawalec and colleagues [6] showed similar results regarding the HRs for the PFS in previously untreated MBC patients. They reported that the combination of TT and endocrine therapy significantly improved PFS in the same patient group and the combination of TT and chemotherapy significantly improved OS in HER2-positive patients. However, in patients with HER2-negative and/or HR-negative disease adding TT to chemotherapy did not improve PFS and OS [6], which contradicted our finding for first-line treatment of HER2-negative and HR-positive patients.

All 13 RCTs included in the review of Kawalec et al were also included in this work and the mean Jadad scores of both reviews were comparable 2.7 (Kawalec et al) versus 3.0 (this

work). However, they did not estimate the median PFS and did not pool overall HRs for all TTs. In addition they only included studies of previously untreated MBC patients, i.e. first-line of treatment [6].

Two other reviews regarding the application of bevacizumab and chemotherapy versus chemotherapy alone included four and seven RCTs, respectively, in their meta-analyses and found HRs for PFS of 0.70 (95% CI 0.64–0.77) and 0.75 (95% CI 0.68–0.84). The results of these reviews were comparable to ours 0.77 (95% CI 0.72–0.82), based on 9 RCTs. All RCTs included in these reviews were also included in our analysis. For the RCTs in these reviews Jadad scores were not available for comparison [54,55].

Another recently published systematic review of Mendes et al [7] concluded that HER2-directed therapies had beneficial impact on OS of patients with HER2-positive MBC. Importantly, they considered only phase III trials and did not estimate the absolute contribution of TTs to PFS and OS in terms of months, or with respect to receptor status of the MBC and line of treatment [7].

TTs and the development of new treatment combinations offer a personalized therapeutic approach of which may be more effective and prolong the life expectancy of MBC patients. However, in the last decades these new therapies account for a substantial increase in healthcare expenditures for MBC treatment and the cost-effectives in terms of monetary units spent per life-year-gained and quality-adjusted life years (QALYs) varies largely [56]. In these analyses the variables that have a significant impact on the cost-effectiveness estimations are the price of the therapies, and the survival benefit and gain in QALYs [57]. Therefore, it is important to assess the effects of TTs in terms of PFS and OS, and QALYs, and to weight them against incurred costs.

This review had several strengths and limitations. To our knowledge, it is the first to estimate median PFS and OS and assess the extent to which TTs contribute to PFS and OS prolongation in terms of months. In addition, it showed pooled HRs for all TTs and per receptor status of the metastatic disease and line of treatment. This review also assessed the quality of the included RCTs by applying the Jadad scale. A limitation of this study was that it used published data from the RCTs to pool HRs and estimate median and range of PFS and OS which could result in an overestimation of the results as studies with unfavorable results

are less often published [58]. Not all publications included in this review reported HRs, PFS and OS or median survival times including ranges. Another limitation was that the HER2-negative patient population was predominantly positive on the ER-status and/or the PR-status, and was reported as being HR-receptor positive in the trials. There were, however, also some HR-negative patients which could have an impact on the estimated survival periods. In addition, studies which evaluated therapies which have not yet been approved by the FDA and/or the EMA for use in metastatic breast cancer (e.g. sorafenib, sunitinib and anti PI3K) were not included. Furthermore, in some of the trials the comparator arm also included TTs which albeit different from the investigational one, might have contributed to the underestimation of the survival periods in the intervention group. Ideally TT should be compared to placebo to evaluate its full potential and impact on PFS and OS. However, such studies were rare to find mainly due to ethical concerns regarding patients' access to treatment.

Conclusion

Estimated HRs show better efficacy of TTs in terms of improved PFS and OS as compared to other therapeutic approaches, and although the gain in median PFS and OS is statistically significant, the absolute numbers are small (3.3 months [0.7–9.6] and 3.5 months [0–4.7]). As the reported data regarding gain in PFS and OS have a relatively large variation, a personalized approach and careful consideration of the patient characteristics, as well as assessment and re-assessment of the receptor status of the primary and metastatic disease should be warranted prior to the application of TT to an individual MBC patient [64]. This seems particularly appropriate as effects in terms of PFS and OS, as well as QALYs, have an impact on costs and cost-effectiveness of TTs in MBC.

Contributors

GHdB and RGKK defined the search strategy and selection criteria. RGKK, MPO and ALR did the literature search and the analysis. All authors contributed to the writing and editing of the manuscript.

Acknowledgements

The authors would like to thank Mrs DG van Ittersum from the Central Library of the University Medical Center Groningen, the Netherlands for developing the search algorithm used in this systematic review.

Funding

None

Disclosure

The authors declare no conflict of interests.

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1 Table 1. Progression-free survival (PFS) and overall survival (OS) in months for non-hormonal
2 targeted therapy (TT) versus comparator therapy (CT) in receptor positive metastatic breast cancer
3 (MBC) disease (38 studies, n=17,192 patients)

4

Reference	Type of RCT	Line of treatment	Receptor status	Targeted (TT) vs. comparator therapy (CT) (number of pts in each arm)	OS months		PFS months		Jadad score
					TT	CT	TT	CT	
HER2-positive and mixed HR status disease									
Pertuzumab and / or trastuzumab containing regimens									
27	LUX-Breast 1 study: phase III	2	HER2-positive	Trastuzumab + vinorelbine (169) VS Afatinib + vinorelbine (339)	28.6	20.5	5.6	5.5	3
16	EGF104900 study: open-label, phase III	2	HER2-positive, 51% ER- and PR-negative	Lapatinib + trastuzumab (146) VS Lapatinib (145)	14	9.5	2.6	1.9	2
24	open-label, phase II	1	HER2-positive, 32-49% ER- and PR-negative, 36% ER- and PR-positive	Paclitaxel + trastuzumab (63) VS Paclitaxel (61)	NA	NA	9.9	6.7	3
28	eLEcTRA study: open label, phase III	1	HER2-positive and HR-positive Sub-group of 35 HER2-negative and HR-positive pts on Letrozole alone	Letrozole + trastuzumab (26) VS Letrozole alone (31/35)	NA	NA	14.1	3.3/15.2	1
31	TAnDEM study: open-label, phase III	1	HER2- and HR-positive	Trastuzumab + anastrozole (103) VS Anastrozole	34.1	28.6	4.8	2.4	3

				(104)					
36	M77001 study: open-label, comparative, phase II	1	HER2-positive, 41-56% ER- and/or PR-positive	Trastuzumab + docetaxel (92) VS Docetaxel alone (94)	31.2	22.7	11.7	6.1	2
45	pivotal, open-label, phase III study	1	HER2-positive	Chemotherapy + trastuzumab (235) VS Chemotherapy (234)	25.4	20.3	7.6	4.6	2
46	CLEOPATRA study: double-blind, placebo-controlled, phase III	1	HER2-positive, 388 pts ER- or PR-positive, 408 pts ER- or PR-negative	Pertuzumab + trastuzumab + docetaxel (402) VS Placebo + trastuzumab + docetaxel (406)	56.5	40.8	18.7	12.4	5
50, 51	A German Breast Group 26/Breast International Group 03-05 study: open-label, phase III	2	HER2-positive (includes LABC)	Trastuzumab + capecitabine (78) VS Capecitabine (78)	24.9	20.6	8.2	5.6	3
Everolimus									
14	BOLERO-3 study: double-blind, placebo-controlled, phase III	2	HER2-positive, 53% ER-positive, 47% ER-negative, 37% PR-positive, 61-62% PR-negative	Everolimus + vinorelbine + trastuzumab (284) VS Placebo + vinorelbine + trastuzumab (285)	NA	NA	7.0	5.8	5
29	BOLERO-1 study: double-blind, placebo-controlled, phase III	1	HER2-positive (includes invasive LRBC), 57% HR-positive, 43 HR-	Everolimus + trastuzumab + paclitaxel (480) VS Placebo + trastuzumab + paclitaxel (239)	NA	NA	15.0	14.5	5

			negative						
Trastuzumab emtansine containing regimens									
30	TDM4450g study: phase II, open-label	1	HER2-positive (includes recurrent LABC), 49-54% ER- and/or PR-positive, 41-48% ER- and PR-negative	Trastuzumab emtansine (67) VS Trastuzumab + docetaxel (70)	NA	NA	14.2	9.2	3
32	TH3RESA study: open-label, phase III	2	HER2-positive, 51-52% ER-positive and/or PR-positive, 43-46% ER-negative and PR-negative	Trastuzumab emtansine (404) VS Treatment of physician's choice (198)	15.8	12	6.2	3.3	3
48	EMILIA study: open-label, phase III	2	HER2-positive (includes LABC), 53-57% ER- and/or PR-positive, 41-45% ER- and/or PR-negative	Trastuzumab emtansine (495) VS Lapatinib plus capecitabine (496)	30.9	25.1	9.4	5.8	3
Lapatinib containing regimens									
19	phase III study	2	HER2-positive, 49-50% ER- and PR-negative, 46-48 ER- and PR-positive, (includes LABC)	Lapatinib + capecitabine (207) VS Capecitabine monotherapy (201)	17.2	14.8	6.1-7.8	4.7-4.9	2

23	MA.31 study: open-label, phase III	1	HER2-positive, 65% ER-positive, 31% ER-negative, 34% PR-positive, 60% PR-negative	Lapatinib + taxane followed by lapatinib (326) VS Trastuzumab + taxane followed by trastuzumab (326)	NA	NA	9.0	11.3	3
26	EGF104535 study: double-blind, placebo-controlled, phase III	1	HER2-positive, ER- and/or PR-positive or unknown	Lapatinib + paclitaxel (222) VS Placebo + paclitaxel (222)	27.8	20.5	9.7	6.5	4
35	NCT00777101 study: open-label, phase II	2	HER2-positive (includes LABC), 40-44% ER-positive, 27-28% PR-positive	Lapatinib + capecitabine (116) VS Neratinib (117)	23.6	19.7	6.8	4.5	2
41	CEREBEL (EGF111438) study: open-label, phase III	2	HER2-positive, 47% ER-positive, 52% ER-negative, 33% PR-positive, 61% PR-negative	Lapatinib + capecitabine (271) VS Trastuzumab + capecitabine (269)	22.7	27.3	6.6	8.1	3
44	EGF30008 study: double-blind, placebo-controlled, parallel group, phase III	1	HER2- and HR-positive	Lapatinib + letrozole (111) VS Letrozole + placebo (108)	33.3	32.3	8.2	3.0	4
Bevacizumab containing regimens									
25	AVEREL study: open-label,	1	HER2-positive (includes	Bevacizumab + trastuzumab + docetaxel (216)	38	38	16.5	13.7	2

	phase III		LRBC), 51-53% ER- and/or PR-positive	VS Trastuzumab + docetaxel (208)					
HR-positive and HER2-negative disease									
Bevacizumab containing regimens									
17	RIBBON-2 study: double-blind, placebo-controlled, phase III	2	HER2-negative (84-85%), HR-positive (72-73%)	Bevacizumab + chemotherapy (459) VS Placebo + chemotherapy (225)	NA	NA	7.2	5.1	4
34	LEA study: open-label, phase III	1	HER2-negative, HR-positive	Endocrine therapy + bevacizumab (191) VS Endocrine therapy (189)	52.1	51.8	19.3	14.4	2
37	AVADO study: double-blind, placebo-controlled	1/2	HER2-negative (includes LRBC), 76-78% ER and PR-positive All groups	Docetaxel + Bevacizumab (7.5 or 15 mg/kg) (248/247) VS Docetaxel + placebo (241)	30.8/30.2	31.9	9.0/10.0	8.1	4
38	phase III study	2	Over 40% ER-positive, over 30% PR-positive, over 20% HER2-positive	Bevacizumab + capecitabine (232) VS Capecitabine (230)	15.1	14.5	4.9	4.2	2
39	E2100 study: open-label, phase III	1/2	Over 90% HER2-negative, over 60% ER-positive, over 50% PR-negative	Paclitaxel + bevacizumab (368) VS Paclitaxel alone (354)	26.7	25.2	11.8	5.9	2
42	open-label phase III study	1	HER2-negative advanced breast cancer	Paclitaxel + bevacizumab (243) VS Paclitaxel + sunitinib (242)	NA	NA	9.2	7.4	4
43	RIBBON-1	1	HER2-	Bevacizumab +	NA	NA	8.6-	5.7-8	2

	study: double-blind, placebo-controlled, phase III		negative (includes LRBC), 74-77% HR-positive	chemotherapy (824) VS Placebo + chemotherapy (413)			9.2		
49	TANIA study: open-label, parallel-group, phase III	2	HER2-negative (includes LRBC), 76-80% ER- and/or PR-positive	Bevacizumab + chemotherapy (247) VS Chemotherapy alone (247)	NA	NA	6.3	4.2	3
Lapatinib containing regimens									
18	CALGB 40302 study: double-blind, placebo-controlled phase III	2	ER-positive and/or PR-positive, 78-84% HER2-negative, 16-21% HER2-positive	Fulvestrant + lapatinib (148) VS Fulvestrant + placebo (147)	30	26.4	4.7	3.8	4
20	EGF30001 study: double-blind, placebo-controlled, phase III	1	HER2-negative/HER2-untested, 44-50% HR-positive	Paclitaxel + lapatinib (291) VS Paclitaxel + placebo (288)	22.8	20.0	6.7	5.3	3
Everolimus containing regimens									
15	GINECO study: open-label, phase II	1/2	HR-positive, 93-98% HER2-negative	Everolimus + tamoxifen (54) VS Tamoxifen alone (57)	NA	32.9	8.6	4.5	2
33	RADAR study: double-blinded, placebo-controlled, phase II, discontinuation study, 8-weeks run-in phase on everolimus	1/2	93% ER and/or PR positive, 7% both ER, PR negative, HER2-negative, patients with bone metastases only	Everolimus (18) VS Placebo (21)	NA	NA	8.5	2.9	3

	prior to randomization								
40, 53	BOLERO-2 study: double-blind, placebo-controlled, phase III,	2	100% ER-positive, 72% PR-positive, HER2-negative	Everolimus + exemestane (485) VS Placebo + exemestane (239)	31.0	26.6	11	4.1	3
52	phase II trial (Sarah Cannon Research Institute), placebo-controlled	1	HER2-negative, 79% ER-positive and/or PR-positive, 21% ER-negative and PR-negative	Everolimus + paclitaxel/carboplatin (56) VS Placebo + paclitaxel/carboplatin (57)	17.5	19.6	9.1	7.1	2
Palbociclib containing regimens									
22	PALOMA-1/TRIO-18: open-label, phase II study	1	ER-positive, HER2-negative	Palbociclib + letrozole (84) VS Letrozole alone (81)	37.5	33.3	20.2	10.2	3
21	PALOMA-2 study: double-blind, phase III	1	ER-positive, HER2-negative	Palbociclib + letrozole (444) VS Placebo + letrozole (222)	NA	NA	24.8	14.5	3
47	PALOMA3 study: double-blind, phase III	2	ER-positive and PR-positive (63.8-68.6%), ER-positive and PR-negative (26.2-27.6%), HER2-negative	Palbociclib + fulvestrant (347) VS Placebo + Fulvestrant (174)	NA	NA	9.2	3.8	5

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Table 2. Median and range of progression-free survival (PFS) and overall survival (OS) in months for non-hormonal targeted therapy (TT) versus comparator therapy (CT) in receptor positive metastatic breast cancer (MBC) disease (38 studies, n=17,192 patients)

	Overall survival – median [range]		**PFS – median [range]**	
	TT	**CT**	**TT**	**CT**
HER2-positive and mixed HR status disease				
Whole subgroup	27.8 [14.0–56.5]	20.6 [9.5–40.8]	8.2 [2.6-18.7]	5.8 [1.9–15.2]
	7.2 [4.5–15.7]		2.4 [0.7–3.5]	
First-line	33.3 [25.4–56.5]	28.6 [20.3–40.8]	10.7 [4.8–18.7]	9.2 [2.4–15.2]
	4.7 [not estimable]		1.5 [not estimable]	
Second-line	23.2 [14.0–30.9]	20.1 [9.5–27.3]	6.7 [2.6–9.4]	5.2 [1.9–8.1]
	3.1 [not estimable]		1.5 [0.7– not estimable]	
Trastuzumab and pertuzumab	28.6 [14.0–56.5]	20.6 [9.5–40.8]	7.6 [2.6–18.7]	5.6 [1.9–15.2]
Trastuzumab emnatasine	23.4 [15.8–30.9]	18.6 [12.0–25.1]	9.4 [6.2–14.2]	5.8 [3.3–9.2]
Lapatinib	23.6 [17.2–33.3]	20.5 [14.8–32.3]	7.5 [6.1–9.7]	5.6 [3.0–11.3]
Everolimus	[not estimable]	[not estimable]	11.0 [7.0–15.0]	10.1 [5.8–14.5]
HR-positive and HER2-negative disease				
Whole subgroup	30.0 [15.1–52.1]	26.4 [14.5–51.8]	9.1 [4.7–24.8]	5.5 [2.9–14.5]
	3.6 [not estimable]		3.6 [1.8–10.3]	
First-line	30.2 [17.5–52.1]	31.9 [19.6–51.8]	9.2 [6.7–24.8]	7.3 [2.9–14.5]
	[not estimable]		2.0 [not estimable]	

Second-line	22.6 [15.1–30.0]	20.5 [14.5–26.4]	6.8 [4.7–11.0]	4.2 [3.8–5.1]
	2.1 [0.6–3.6]		2.6 [0.9–5.9]	
Bevacizumab	30.2 [15.1–52.1]	28.6 [14.5–51.8]	9.1 [4.9–19.3]	5.9 [4.2–14.4]
Lapatinib	26.4 [22.8–30.0]	23.2 [20.0–26.4]	5.7 [4.7–6.7]	4.6 [3.8–5.3]
Everolimus	[not estimable]	[not estimable]	8.9 [8.5–11.0]	4.3 [2.9–7.1]
Palbociclib	[not estimable]	[not estimable]	20.2 [9.2–24.8]	10.2 [3.8–14.5]
All subgroups	28.6 [14.0–56.5]	25.1 [9.5–51.8]	9.0 [2.6–24.8]	5.7 [1.9–15.2]
Overall increase	3.5 [0–4.7]		3.3 [0.7–9.6]	

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Figure 1. Flow diagram

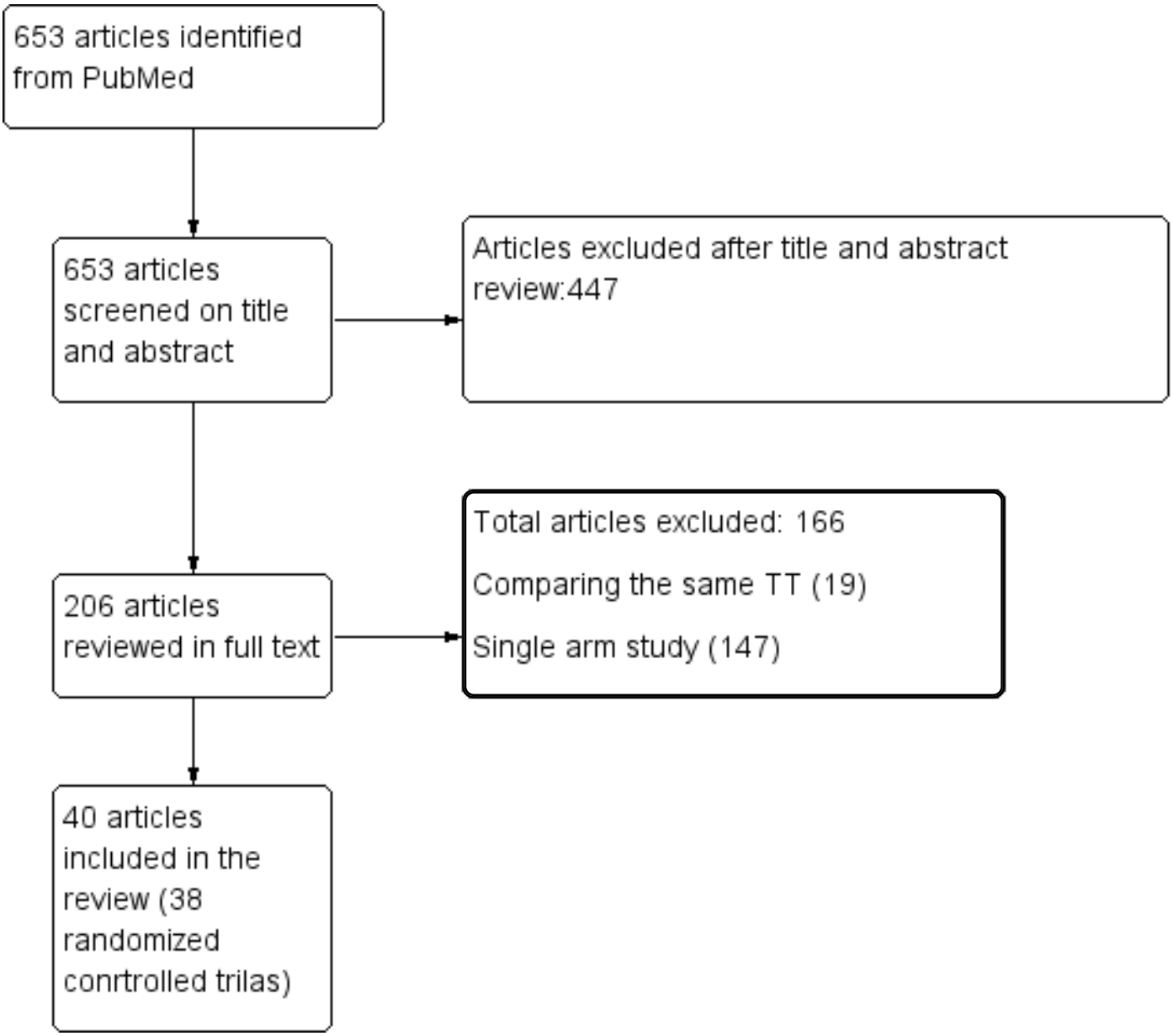


Figure 2. Progression free survival - Forest plot

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
1.1.1 HER2-positive and mixed HR status disease, 1st line of treatment				
Gelmon 2015 [23]	0.3115	0.0966	3.9%	1.37 [1.13, 1.65]
Gianni 2013 [25]	-0.1985	0.1185	2.6%	0.82 [0.65, 1.03]
Guan 2013 [26]	-0.6539	0.109	3.0%	0.52 [0.42, 0.64]
Huober 2012 [28]	-0.3976	0.3328	0.3%	0.67 [0.35, 1.29]
Huober 2012 [28]	-0.3474	0.1564	1.5%	0.71 [0.52, 0.96]
Hurvitz 2013 [30]	-0.5276	0.2521	0.6%	0.59 [0.36, 0.97]
Hurvitz 2015 [29]	-0.1189	0.0999	3.6%	0.89 [0.73, 1.08]
Kaufman 2009 [31]	-0.462	0.1495	1.6%	0.63 [0.47, 0.84]
Schwartzberg 2010 [44]	-0.3425	0.1492	1.6%	0.71 [0.53, 0.95]
Slamon 2001 [45]	-0.6733	0.1114	2.9%	0.51 [0.41, 0.63]
Swain 2015 [46]	-0.3857	0.0812	5.5%	0.68 [0.58, 0.80]
Von Minckwitz 2014 [49]	-0.2877	0.1054	3.3%	0.75 [0.61, 0.92]
Subtotal (95% CI)			**30.4%**	**0.74 [0.70, 0.80]**
Heterogeneity: Chi² = 69.22, df = 11 (P < 0.00001); I² = 84%				
Test for overall effect: Z = 8.57 (P < 0.00001)				
1.1.2 HER2-positive and mixed HR status disease, 2nd and beyond line of treatment				
André 2014 [14]	-0.2485	0.093	4.2%	0.78 [0.65, 0.94]
Blackwell 2012 [16]	-0.3011	0.1243	2.3%	0.74 [0.58, 0.94]
Cameron 2010 [19]	-0.6931	0.1968	0.9%	0.50 [0.34, 0.74]
Cameron 2010 [19]	-0.4463	0.266	0.5%	0.64 [0.38, 1.08]
Harbeck 2016 [27]	0.0964	0.1261	2.3%	1.10 [0.86, 1.41]
Krop 2014 [32]	-0.6349	0.1187	2.6%	0.53 [0.42, 0.67]
Martin 2013 [35]	0.1767	0.1496	1.6%	1.19 [0.89, 1.60]
Pivot 2015 [41]	0.267	0.1162	2.7%	1.31 [1.04, 1.64]
Verma 2012 [48]	-0.4308	0.0852	5.0%	0.65 [0.55, 0.77]
Von Minckwitz 2009 [51]	-0.3783	0.1793	1.1%	0.69 [0.48, 0.97]
Subtotal (95% CI)			**23.2%**	**0.79 [0.73, 0.85]**
Heterogeneity: Chi² = 56.74, df = 9 (P < 0.00001); I² = 84%				
Test for overall effect: Z = 6.11 (P < 0.00001)				
1.1.3 HR-positive and HER2-negative disease, 1st line of treatment				
Bachelot 2012 [15]	-0.6162	0.2069	0.8%	0.54 [0.36, 0.81]
Di Leo2008 [20]	-0.1393	0.0966	3.9%	0.87 [0.72, 1.05]
Finn 2015 [22]	-0.7174	0.2169	0.8%	0.49 [0.32, 0.75]
Finn 2016 [21]	-0.5525	0.1143	2.8%	0.58 [0.46, 0.72]
Maass 2013 [33]	-0.5906	0.3445	0.3%	0.55 [0.28, 1.09]
Martín 2015 [34]	-0.1863	0.1247	2.3%	0.83 [0.65, 1.06]
Miles 2010 [37]	-0.2594	0.0953	4.0%	0.77 [0.64, 0.93]
Miles 2010 [37]	-0.1446	0.0938	4.1%	0.87 [0.72, 1.04]
Miller 2007 [39]	-0.5108	0.0829	5.3%	0.60 [0.51, 0.71]
Robert 2011 [42]	0.4886	0.1648	1.3%	1.63 [1.18, 2.25]
Robert 2011 [43]	-0.4463	0.1059	3.2%	0.64 [0.52, 0.79]
Robert 2011 [43]	-0.3771	0.1034	3.4%	0.69 [0.56, 0.84]
Yardley 2015 [52]	-0.0363	0.2421	0.6%	0.96 [0.60, 1.55]
Subtotal (95% CI)			**32.8%**	**0.73 [0.69, 0.78]**
Heterogeneity: Chi² = 51.09, df = 12 (P < 0.00001); I² = 77%				
Test for overall effect: Z = 9.33 (P < 0.00001)				
1.1.4 HR-positive and HER2-negative disease, 2nd and beyond line of treatment				
Brufsky 2011 [17]	-0.2485	0.1009	3.6%	0.78 [0.64, 0.95]
Burstein 2014 [18]	0.0392	0.1213	2.5%	1.04 [0.82, 1.32]
Miller 2005 [38]	-0.0202	0.123	2.4%	0.98 [0.77, 1.25]
Turner 2015 [47]	-0.8675	0.1387	1.9%	0.42 [0.32, 0.55]
Yardley 2013 [53]	-0.9676	0.1039	3.3%	0.38 [0.31, 0.47]
Subtotal (95% CI)			**13.6%**	**0.66 [0.59, 0.73]**
Heterogeneity: Chi² = 65.97, df = 4 (P < 0.00001); I² = 94%				
Test for overall effect: Z = 8.13 (P < 0.00001)				
Total (95% CI)			**100.0%**	**0.74 [0.71, 0.77]**
Heterogeneity: Chi² = 250.59, df = 39 (P < 0.00001); I² = 84%				
Test for overall effect: Z = 16.01 (P < 0.00001)				
Test for subgroup differences: Chi² = 7.57, df = 3 (P = 0.06), I² = 60.3%				

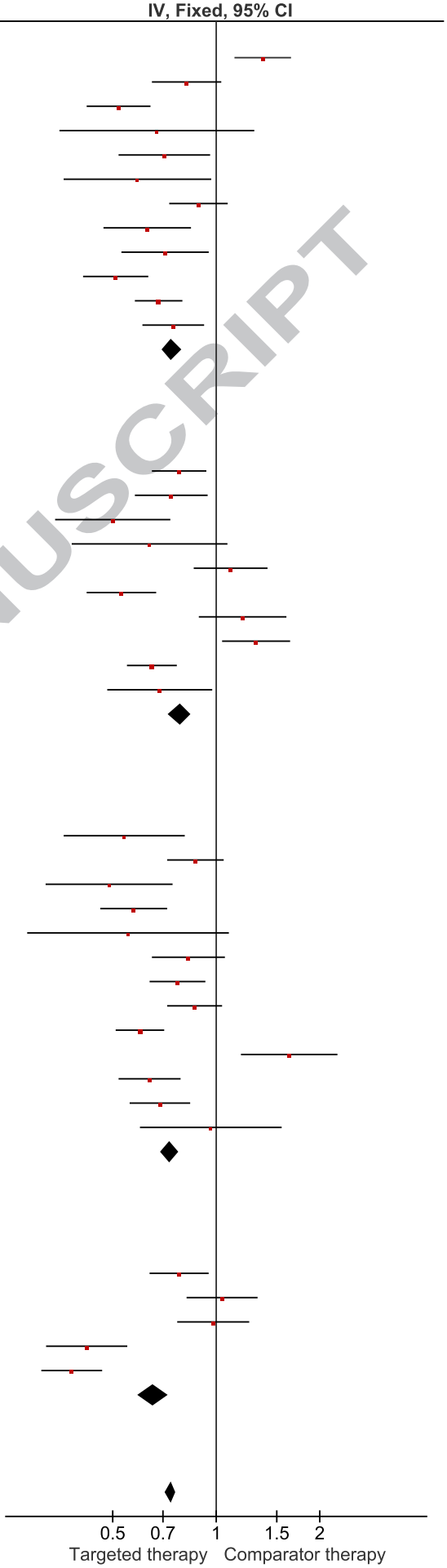
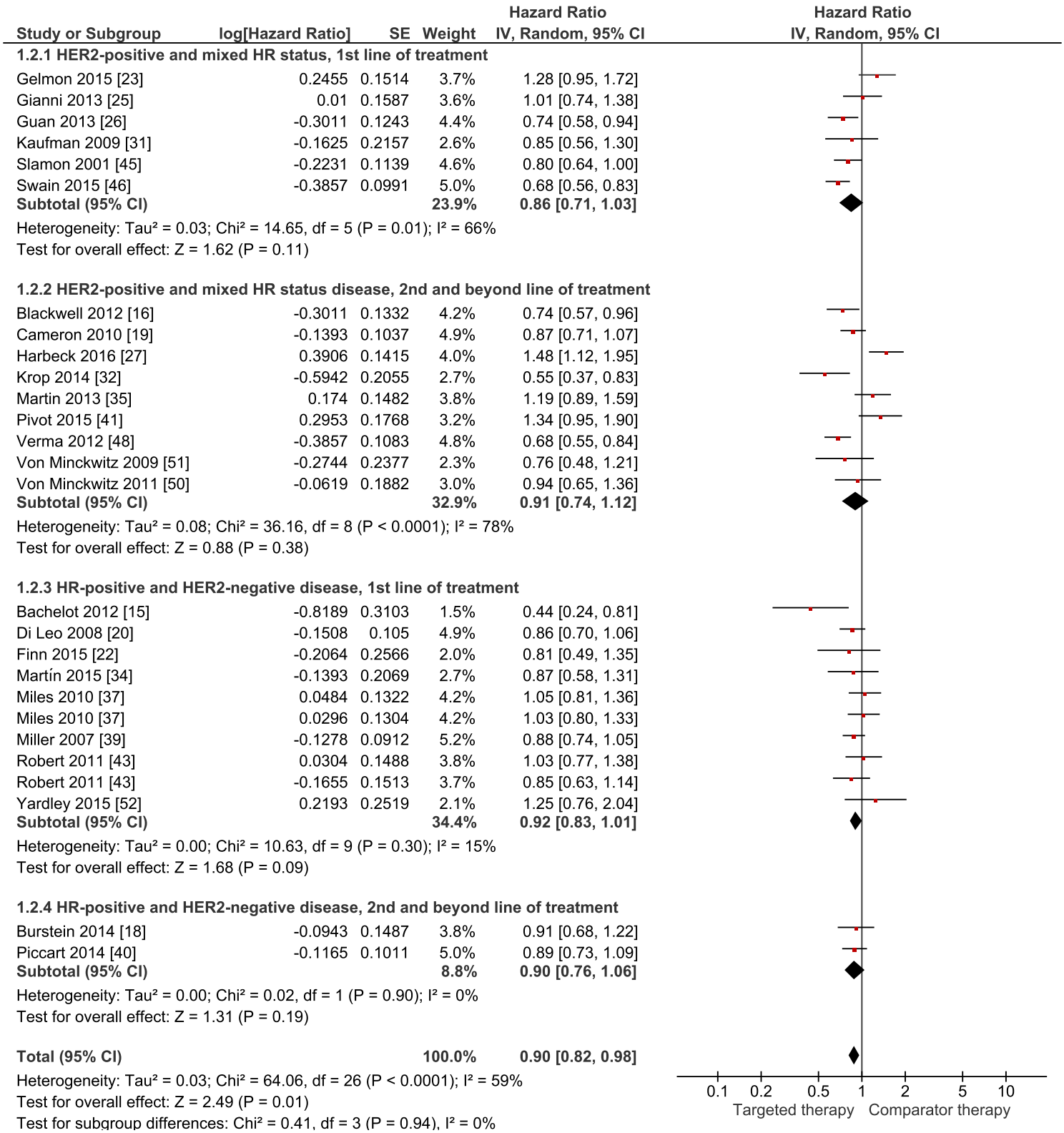


Figure 3. Overall survival - Forest plot



Conflict of interest statement:

Authors have disclosed no conflicts of interest.

Highlights:

- Non-hormonal targeted therapies demonstrated better efficacy as compared to other treatments.
- Non-hormonal targeted therapies could potentially prolong progression-free and overall survival in metastatic breast cancer patients with positive receptor status of the disease.
- As pooled data suggests large variation in survival a prior selection of patients for therapy based on their receptor status is warranted and could provide personalized treatment management.